REMARKS

Claims 1-8, 10-38 and 40-54 remain pending herein. Claims 9 and 39 have been withdrawn from further consideration. Claims 7, 8, 12-14, 16-18, 22-23 and 25-37 have been amended. New claims 40-54 have been added. Reconsideration of the pending claims is requested.

Claims 7-8 and 16-17 stand objected to due to the use of parenthetical expressions. Applicants have deleted the parenthetical expressions since they are preceded by the corresponding definitions thereof. Therefore, the corresponding definitions of the parenthetical expressions remain in the claims. Applicants submit that this objection has been overcome and request that it be withdrawn.

Claim 25 stands objected to as being of improper dependent form or for failing to limit the subject matter of a previous claim. Claim 25 has been amended to require that the indicated therapeutic plasma level occurs in a subject to which the dosage form is administered. The term "generally" has also been removed from the claim. Applicants submit that this objection has been overcome and request that it be withdrawn.

Claims 26-37 have been amended to require that release of the drugs occurs after exposure to an aqueous environment, which includes any water-based fluid such as, for example, an assay solution or a body fluid as indicated in the specification.

Claims 7-8, 12, 14, 16-18, 22-23, 28-29 and 31-37 stand rejected under 37 C.F.R. §112, 2nd para. as being indefinite or for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Insofar as it may apply to the present claims, the rejection is respectfully traversed.

Claims 7-8 and 16-17 have been amended to delete the trademarks and parenthetical expressions.

Claim 12 includes the terms "controlled, delayed, sustained, immediate, timed, slow or rapid release". Claim 18 includes the term "rapidly". Claim 29 includes the terms "rapid, immediate, controlled, sustained, slow, timed, targeted, pseudo-first order, first order, pseudo-zero order, zero-order, and/or delayed release". Claims 30-33 include various combinations of the terms "controlled" and "rapid" release. Claims 34 and 36 include the term "delayed but rapid release". Claims 35 and 37 include the term "timed but controlled release".

Applicants note that the artisan of ordinary skill recognizes and understands the scope and definition of these commonly used terms as they relate to pharmaceutical dosage forms and pharmaceutical compositions. These terms are generally defined in textbooks widely used in the pharmaceutical industry and colleges of Pharmacy. These terms concern either the rate at which or the manner in which drug is released from a dosage form or composition. Applicants note that hundreds of issued US patents include these very terms in their respective claims. Moreover, the instant specification also includes examples of dosage forms that exhibit these types of drug release profiles.

A controlled release dosage form provides a controlled release of drug therefrom. Although not limited to any particular period of time, a controlled release dosage form generally releases drug over a period of about three hours up to a day, week or month, for example.

A delayed release dosage form is one that exhibits an initial delay in the release of drug after exposure to an environment of use. The period of delay is generally anywhere from minutes to hours.

A sustained release dosage form is one that provides a sustained release of drug over an extended period of time. The term "sustained release" is sometimes used synonymously with the terms "controlled release" or "extended release"; however, a sustained release dosage form generally provides a relatively constant rate of release for a period of hours, days or weeks.

An immediate release dosage form is one that begins to release drug shortly, generally seconds to minutes, after exposure to an environment of use and therefore does not exhibit a significant delay in release of drug.

A timed release dosage form is one that begins to release drug after a predetermined period of time as measured from the moment of initial exposure to the environment of use.

A slow release dosage form is one that provides a slow rate of release of drug so that drug is released over a period of hours to days.

A rapid release dosage form is one that releases drug over a period of minutes to hours once release has begun.

A targeted release dosage form generally refers to an oral dosage form that designed to deliver drug to a particular portion of the gastrointestinal tract of a subject. An exemplary targeted dosage form is an enteric dosage form that delivers a drug into the middle to lower intestinal tract but not into the stomach or mouth of the subject.

A pseudo-first order release profile is one that approximates a first order release profile. A first order release profile characterizes the release profile of a dosage form that releases a constant percentage of an initial drug charge per unit time.

A pseudo-zero order release profile is one that approximates a zero-order release profile. A zero-order release profile characterizes the release profile of a dosage form that releases a constant amount of drug per unit time.

A delayed but rapid release dosage form is one that provides a delayed release of a drug followed by a rapid release of the drug. In other words, the rapid release of drug is delayed by a period of time.

A delayed but controlled release dosage form is one that provides a delayed release of a drug followed by a controlled release of the drug. In other words, the controlled release of drug is delayed by a period of time.

Accordingly, Applicants submit that the use of these terms in the claims does not render the claims indefinite since these terms are widely used in the pharmaceutical industry and their definitions are well known by the artisan of ordinary skill.

Claim 14 has been rewritten to clarify the language thereof. The claim now requires a "period of time sufficient to enhance the therapeutic benefit provided by the COX-II inhibitor." Applicants submit that this language is clear and distinctly claims the invention. Applicants note that the phrase "a period of time sufficient" is widely used in the claims of U.S. patents concerning the pharmaceutical sciences. Moreover, the artisan of ordinary skill understands the meaning of that phrase. Claim 14 now covers a dosage form that provides therapeutically effective amounts of the muscle relaxant, wherein the amounts of muscle relaxant are sufficient to enhance the therapeutic benefit of the COX-II inhibitor, as compared to the therapeutic benefit provided by the COX-II inhibitor when it is administered alone. The minimum period for which the dosage form must provide the therapeutic levels of the muscle relaxant is that period of time which is measured beginning with the time of administration of the dosage form and ending with the time at which a positive determination of enhancement of therapeutic benefit is made. Of course, the period of time can exceed the just-described minimum period.

Claims 22 and 23 include the terms "one drug" and "other drug". The claims have been amended to clarify the antecedent bases of the terms.

Accordingly, Applicants respectfully submit that the rejection of claims 7-8, 12, 14, 16-18, 22-23, 28-29 and 31-37 under 37 C.F.R. §112, 2nd para. has been overcome and request that it be withdrawn.

Claims 1-8 and 10-38 stand rejected under 37 C.F.R. §103(a) as being unpatentable over Burch et al. Insofar as it may apply to the present claims, this rejection is respectfully traversed.

Examiner states that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a COX-II inhibitor, such as rofecoxib, in combination with a muscle relaxant, such as pridinol, in a pharmaceutical composition or dosage. Examiner also states that individual use of COX-II inhibitors and muscle relaxants for the treatment of pain is known and that the combined use of pridinol with other analgesics for the treatment of pain is known. Finally, examiner states that it is considered *prima facie* obvious to combine these components into a composition for the treatment of pain and "at least additive therapeutic effects would have been reasonably expected." Applicants respectfully disagree.

It is well known that drugs used in the same therapeutic area or even for treating the same indication cannot always be combined *a priori* with the expectation of at least additive therapeutic effects. The scientific literature is full of examples wherein compounds of different classes, which are used to treat the same indication, cannot be combined into safe and efficacious dosage forms thereby resulting in incompatible drug combinations. The reasons for this unexpected lack of compatibility are varied; however, it is often found that the incompatible drug combinations result in increased side effects, unwanted drug interactions or new side effects. More specifically, in the area of analgesia, there are analgesic drug combinations that are contraindicated for some or all of these very same reasons. Accordingly, one of ordinary skill in the art would not necessarily have been motivated to employ a COX-II inhibitor in combination with a muscle relaxant in a pharmaceutical composition or dosage.

The claimed combination provides an unexpectedly enhanced analgesic therapeutic benefit. Attached hereto is a declaration under 37 C.F.R.§1.132 by Dr. Feleder of Osmotica Corp., the assignee of the present application. The declaration includes Dr. Feleder's comments regarding the use of combination analgesic therapy in the treatment of pain and pain related disorders. The state of the art indicates that one of ordinary skill will not necessarily expect at least an additive analgesic effect upon the combined administration of a two analgesic compounds. Included with the declaration are abstracts of several different scientific literature

publications published in peer reviewed and well recognized scientific journals. In brief, the publications establish the unpredictability of results in the area of combined administration of analgesic compounds of different classes. The scientific publications include some combinations that provide no enhanced or additive analgesic effect and other combinations that provide an additive or synergistic analgesic effect. Moreover, some combinations provide increased incidence or severity of side effects. Therefore, the artisan of ordinary skill would not necessarily expect the combined administration of a COX-II inhibitor and a muscle relaxant to yield an enhanced analgesic effect, let alone an additive or even synergistic analgesic effect.

Accordingly, the claimed combination is not *prima facie* obvious and is therefore patentable over the art of record. In view of the above, applicants submit that the rejection of claims 1-8 and 10-38 under 37 C.F.R.§103(a) has been overcome and request that it be withdrawn.

New claim 40 covers a pharmaceutical composition comprising a COX-II inhibitor selected from a defined group (See original claim 8), a muscle relaxant selected from a defined group (See original claim 7), and at least one pharmaceutical excipient. Claim 41 limits the types of pharmaceutical excipients (See page 22, lines 24-28). Claim 42 limits the weight ratio of COX-II inhibitor to muscle relaxant (See claim 38). Claims 43-45 require the drugs to be present in specified release forms (See claims 29, 34-37). Claim 46-48 covers pharmaceutical dosage forms comprising previously defined pharmaceutical compositions. New claim 49 covers a pharmaceutical composition comprising (rofecoxib or celecoxib), pridinol and at least one pharmaceutical excipient (See pages 31-42). Claim 50 limits the pharmaceutical excipient of claim 49. Claim 51 limits the weight ratio of the COX-II to pridinol. Claims 52 and 54 limit the type of form in which the drugs are provided. Claim 53 requires that at least one of the drugs also be provided in delayed or targeted release form. None of the cited art discloses or suggests a pharmaceutical composition or dosage form as claimed.

A "Marked-up Version of the Claims" and "Clean Version of the Claims" as amended are attached hereto. Entry into the record of the amendments indicated thereon is requested. Applicants respectfully request entry of this Response into the record and full consideration thereof.

In view of all the foregoing, Applicants respectfully submit that the claims are patentable over the art of record and in form for allowance. An early notice of allowance thereof is requested.

Respectfully submitted,

Date: 12/20/01

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Docket No. PHUS-28

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of: §
FAOUR, J. et al. §
§
Serial No.: 09/770,901 § Group Art Unit: 1617
Filed: January 26, 2001 § Examiner: Shaojia A. Jiang

For: Pharmaceutical compositions containing A COX-II inhibitor and a muscle relaxant

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on 12/20/01.

Rick Matos
Typed or printed name of person mailing paper

Signature of person mailing paper

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER RULE 37 C.F.R.§1.132

Further to the Office Action mailed September 28, 2001, the undersigned hereby declares as follows:

My name is Ethel C. Feleder. I reside in Luis María Campos 449, 2° A, Buenos Aires, Argentina.

I am knowledgeable in the area of Internal Medicine, Basic and Clinical Pharmacology and in particular in the area of the clinical evaluation of pharmaceutical formulations. My education, experience, publications and awards are summarized in my curriculum vitae, which is attached.

I am familiar with the subject matter of the invention disclosed and claimed in the above-identified patent application. In particular, I am familiar with conventional methods of analgesic therapy with individual drugs and with combinations of drugs.

With regard to the subject matter of claims 1-8, 40-45 and 49-54, I understand that the claims cover a pharmaceutical composition comprising a COX-II inhibitor and a muscle relaxant.

With regard to the subject matter of claims 10-38 and 46-48, I understand that the claims cover a pharmaceutical dosage form comprising a COX-II inhibitor and a muscle relaxant.

As a medical doctor, it is my belief that the claimed pharmaceutical compositions and dosage forms provide significant advantages over conventional analgesic compositions and dosage forms used in pain therapy. In particular, the claimed pharmaceutical composition and dosage form provide an

enhanced analgesic affect as compared to the administration of either agent alone. The exemplary formulation of rofecoxib and pridinol, the claimed composition and the claimed dosage form should also provide at least an additive analgesic effect.

Conventional analgesic therapy generally involves administration of a pharmaceutical composition containing one or two different analgesic drugs. However, not all combinations of analgesic drugs are more suitable, in terms of safety or efficacy, than the administration of a single product. Furthermore, the additivity of the analgesic effect of analgesic drugs cannot be predicted *a priori*. For example, M. R. Naidu et al. (*Pharmacotherapy* (1994), Mar-Apr., 14(2), pp. 173-177) report that the administration of ketorolac alone is superior in terms of analgesia to the combined administration of ibuprofen and paracetamol in the same or different dosage forms for the relief of postoperative. In addition, R. Dionne (*Compend. Contin. Educ. Dent.* (2000) July, 21(7), pp. 572-574 and 576-577) reports that the combination of an opioid with acetaminophen or aspirin does not provide greater analgesia but results in a higher incidence of side effects such as drowsiness and nausea. Moreover, S. Ilkjaer et al. (*Acta Anaesthesiol. Scand.* (2000), Aug., 44(7), pp. 873-877) report that the combination of ibuprofen with dextromethorphan provides no additive analgesic effect. Therefore, one of ordinary skill in the art would not necessarily *a priori* consider any and all combinations of analgesics to be suitable combinations or even consider that all analgesic combinations would result in additive analgesic effects.

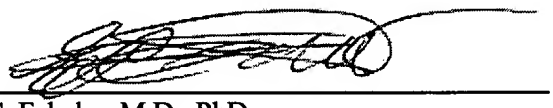
The discovery or expectation of a synergistic analgesic effect from a combination of analgesic drugs or drug classes is also unpredictable. G. L. Wideman et al. (*Clin. Pharmacol. Ther.* (1999), Jan., 65(1), pp. 66-76) report that, when hydrocodone is administered with ibuprofen to a subject for the treatment of postoperative pain, an additive and not synergistic analgesic effect is found. R. A. Dionne (*J. Oral Maxillofac. Surg.* (1999), June, 57(6), pp. 673-678) reports that the combined administration of an nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen, and an orally effective opioid analgesic (such as oxycodone) to patients for the treatment of post-operative oral surgery provides an additive and not synergistic analgesic effect. S.M. Siddik et al. (*Reg. Anesth. Pain Med.* (2001), July-Aug., 26(4), pp. 310-315) report the results of a comparative study on the analgesic effects provided by morphine in combination with propacetamol and/or diclofenac. The combination of diclofenac and morphine provides improved analgesia and resulted in reduced morphine demand, whereas the combination of propacetamol and morphine did not improve analgesia or reduce the demand for morphine significantly. In addition, the combination of diclofenac, propacetamol and morphine did not even provide an additive analgesic effect.

Therefore, it is truly unexpected that the combined administration of a COX-II inhibitor and a muscle relaxant provides an improved, additive or synergistic analgesic effect when administered to a subject as compared to the analgesic effect provided by the administration of either agent alone.

I further declare that the statements made herein, to my knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 12/20/2001



Ethel C. Feleder, M.D., PhD

ACCESSION NUMBER: 94:605521 SCISEARCH
THE GENUINE ARTICLE: ND068
TITLE: EVALUATION OF **KETOROLAC**, IBUPROFEN-PARACETAMOL, AND DEXTROPROPOXYPHENE-PARACETAMOL IN POSTOPERATIVE PAIN
AUTHOR: **NAIDU M U R (Reprint)**; KUMAR T R; JAGDISHCHANDRA U S; BABU P A; RAO M M; BABHULKAR S S; RAO P T; RISBUD Y; SHAH R
CORPORATE SOURCE: NIZAMS INST MED SCI, DEPT CLIN PHARMACOL & THERAPEUT, HYDERABAD 500482, INDIA (Reprint); NIZAMS INST MED SCI, DEPT ANESTHESIOL, HYDERABAD 500482, INDIA; INDIRIA GANDHAI MED COLL, DEPT ORTHOPAED, NAGPUR, INDIA; SCB MED COLL, CUTTACK Z0UYFK1ZCUTT, INDIA; MR MED COLL, GULBARGA, INDIA; SASSON HOSP, POONA, INDIA
COUNTRY OF AUTHOR: INDIA
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FILE SEGMENT: CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 14

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Study Objective. To compare the analgesic efficacy of **ketorolac**, ibuprofen-paracetamol (acetaminophen), and dextropropoxyphene-paracetamol in postoperative pain.

Design. Randomized, double-blind, parallel, single-dose study.

Setting. Multicenter, with five centers participating.

Patients. One hundred sixty patients with moderate to severe postoperative pain requiring oral analgesics were enrolled. Seventeen patients were excluded from final analysis due to deviation from protocol.

Interventions. **Ketorolac** tromethamine 10 mg, a combination of ibuprofen 400 mg plus paracetamol 325 mg, or a combination of dextropropoxyphene 65 mg plus paracetamol 400 mg was given orally to patients with moderate to severe baseline pain.

Measurements and Main Results. Pain intensity and pain relief scores were rated at baseline, at 30 minutes, and hourly to 6 hours. Until the end of first hour, analgesia was similar for all three regimens. **Ketorolac** had a significantly higher analgesic effect than the two combinations between hours 2 and 6. Analgesia was similar for the two combinations. For all three test drugs the frequency of adverse effects was similar.

Conclusions. **Ketorolac** 10 mg is a superior analgesic to ibuprofen-paracetamol or dextropropoxyphene-paracetamol in the treatment of postoperative pain.

Compend Contin Educ Dent 2000 Jul;21(7):572-4, 576-7

Additive analgesia without opioid side effects.

Dionne R.

National Institute of Dental and Craniofacial Research, Bethesda, Maryland, USA.

Postoperative pain control is often inadequate because of insufficient pain relief or unacceptable side effects. Nonsteroidal antiinflammatory drugs (NSAIDs) are very efficacious for pain of dental origin, but their ceiling of efficacy does not result in greater peak analgesia if the dose is raised beyond recommended limits. Switching to an opioid combined with acetaminophen or aspirin does not result in greater analgesia, but increases the incidence of side effects such as drowsiness and nausea. Combining NSAIDs with opioids has been largely unsuccessful and still results in opioid side effects. The combination of NSAIDs with acetaminophen holds promise for greater analgesia than either drug alone, but without the increased side effects associated with opioids in ambulatory dental patients.

Acta Anaesthesiol Scand 2000 Aug;44(7):873-7

The effect of dextromethorphan, alone or in combination with ibuprofen, on postoperative pain after minor gynaecological surgery.

Ilkjaer S, Nielsen PA, Bach LF, Wernberg M, Dahl JB.

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BACKGROUND: Experimental studies have demonstrated that peripheral tissue injury may lead to hyperexcitability of nociceptive neurones in the dorsal horn, in part mediated by N-methyl-D-aspartate (NMDA)-receptor mechanisms. Sensitisation of dorsal horn neurones may be an important contributor to postoperative pain. The aim of the present study was to investigate the effect of the NMDA-receptor antagonist dextromethorphan on pain after minor gynaecological surgery, and to evaluate a potential additive effect with ibuprofen. METHODS: In a double-blind, placebo-controlled study, 100 patients scheduled for elective termination of pregnancy were randomised to receive placebo, oral ibuprofen 400 mg, oral dextromethorphan 120 mg, or a combination of ibuprofen 400 mg and dextromethorphan 120 mg, 1 h before surgery. Pain and analgesic requirements were assessed 0.5, 1 and 2 h after operation. RESULTS: We observed no effect of dextromethorphan on visual analogue scale (VAS) pain scores or analgesic consumption, and no additive or synergistic analgesic effects between ibuprofen and dextromethorphan. Ibuprofen reduced pain scores compared with placebo, and analgesic consumption compared with both placebo and dextromethorphan. The combination of ibuprofen and dextromethorphan increased preoperative nausea compared with both placebo and ibuprofen, whereas no statistically significant side effects were observed with dextromethorphan alone. CONCLUSION: No analgesic effects of oral dextromethorphan 120 mg on pain after surgical termination of labour, and no additive analgesic effects when combined with ibuprofen 400 mg, were observed. Ibuprofen reduced both VAS pain scores and analgesic consumption compared with placebo.

: Clin Pharmacol Ther 1999 Jan;65(1):66-76

Analgesic efficacy of a combination of hydrocodone with ibuprofen in postoperative pain.

Wideman GL, Keffer M, Morris E, Doyle RT Jr, Jiang JG, Beaver WT.

Brookwood Medical Center, Birmingham, AL, USA.

Two randomized, double-blind, parallel-group single-dose 2 x 2 factorial analgesic studies compared a single-dose or a 2-tablet dose of a combination of 7.5 mg hydrocodone bitartrate with 200 mg ibuprofen with each constituent alone and with a placebo in women with moderate or severe postoperative pain from abdominal or gynecologic surgery. A nurse-observer recorded patient reports of pain intensity and pain relief periodically for 8 hours. In both studies, the combination was significantly superior to placebo for sum of the pain intensity differences (SPID), total pain relief (TOTPAR), peak pain intensity difference (PID) and pain relief, global evaluation, and time to remedication. The combination was likewise significantly superior to both hydrocodone and ibuprofen for most of these summary measures of analgesia. In a factorial analysis, both the hydrocodone and ibuprofen effects were significant for most summary measures of analgesia, whereas results of the interaction contrast were consistent with the concept that the analgesic effect of the combination represents the additive analgesia of its 2 constituents.

J Oral Maxillofac Surg 1999 Jun;57(6):673-8

Additive analgesic effects of oxycodone and ibuprofen in the oral surgery model.

Dionne RA.

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PURPOSE: A traditional approach to achieve greater analgesic efficacy is to combine an efficacious dose of a nonopioid with a dose of an opioid sufficient to produce additive analgesia without a substantial increase in the incidence of adverse effects. This study evaluated the additive analagesic effects of the combination of ibuprofen and oxycodone. PATIENTS AND METHODS: A dose of 400 mg ibuprofen was compared with 400 mg ibuprofen with oxycodone in doses of 2.5, 5, or 10 mg in the oral surgery model of acute pain. Analgesic efficacy was measured with category and visual analog scales at 15, 30, 45, and 60 minutes and hourly up to 6 hours. RESULTS: Ibuprofen plus 10 mg oxycodone produced significantly greater analgesia compared with the other three groups, as measured by the visual analog scale from 15 minutes after drug administration up to the 2-hour observation. All four treatments were similar from 3 to 6 hours, with the area under the pain intensity difference curve being similar across groups. Neither the 2.5-mg nor the 5-mg oxycodone dose provided any additive analgesia over ibuprofen at any points. Addition of oxycodone resulted in a dose-related increase in the number of patients reporting adverse effects, with significantly greater drowsiness and vomiting at the 10-mg dose. CONCLUSIONS: These results indicate that additive analgesia can be achieved for the combination of a nonsteroidal anti-inflammatory drug and an orally effective opioid, with faster onset of relief for the combination of 400 mg ibuprofen and 10 mg oxycodone over the first 2 hours after administration, but at the expense of an increased incidence of adverse events.

Reg Anesth Pain Med 2001 Jul-Aug;26(4):310-5

Comment in:

- Reg Anesth Pain Med. 2001 Jul-Aug;26(4):298-300. UI: 21357114

Reg Anesth Pain Med

Diclofenac and/or propacetamol for postoperative pain management after cesarean delivery in patients receiving patient controlled analgesia morphine.

Siddik SM, Aouad MT, Jalbout MI, Rizk LB, Kamar GH, Baraka AS.

Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

BACKGROUND AND OBJECTIVES: A multimodal approach to postcesarean pain management may enhance analgesia and reduce side effects after surgery. This study evaluates the postoperative analgesic effects of propacetamol and/or diclofenac in parturients undergoing elective cesarean delivery under spinal anesthesia. METHODS: After randomization, 80 healthy parturients received the following: placebo (group M), 100 mg diclofenac rectally every 8 hours (group MD), 2 g propacetamol intravenously every 6 hours (group MP), or a combination of 2 g propacetamol and 100 mg diclofenac (group MDP) as described above. Drugs were administered for 24 hours after surgery. Postoperative pain was controlled with a patient controlled analgesia pump, using morphine. The visual analog scale (VAS) at rest and on coughing, as well as the morphine consumption, were evaluated at 2, 6, and 24 hours postoperatively. Also, the side effects experienced after undergoing the different regimens were compared. RESULTS: The patients' characteristics did not differ significantly between the 4 groups. VAS score at 2 hours, both at rest and on coughing were lower in group MDP and MD compared with group M (P `.05). At 24 hours, there was still a tendency toward lower pain scores in the groups MDP and MD; however, this difference was only statistically significant at rest between the MDP group and the MP and M groups. Morphine consumption at 2, 6, and 24 hours was lower in the MDP and MD groups compared with the MP and M groups (P <.05). The morphine-sparing effect was higher in groups MDP and MD compared with group MP (57% and 46%, respectively, v 8.2%, P <.05). The incidence of side effects was similar in all groups. However, the power of the study was too low to permit an evaluation of potential side effects. CONCLUSION: Diclofenac after cesarean delivery improves analgesia and has a highly significant morphine-sparing effect. We were unable to demonstrate significant morphine-sparing effect of propacetamol or additive effect of propacetamol and diclofenac in this group of patients.

CLAIMS

We claim:

1) A pharmaceutical composition comprising:
   a) a COX-II inhibitor;
   b) a muscle relaxant; and
   c) at least one pharmaceutical excipient.
2) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor binds COX-II receptors selectively over COX-I receptors.
3) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor binds COX-II receptors specifically.
4) The pharmaceutical composition of claim 1, wherein the weight ratio of COX-II inhibitor to muscle relaxant varies from (12.5:2.2) to (50:8).
5) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor is selected from the group consisting of central muscle relaxants and neuromuscular blocking agents.
6) The pharmaceutical composition of claim 1, wherein the at least one pharmaceutical excipient is independently selected from the group consisting of an acidifying agent, adsorbents, alkalizing agent, antioxidants, buffering agent, colorant, flavorant, sweetening agent, tablet antiadherent, tablet binder, tablet and capsule diluent, tablet direct compression excipient, tablet disintegrant, tablet glidant, tablet lubricant, tablet or capsule opaquant, plasticizer, surface active agent, solvent, oil, soap, detergent, and tablet polishing agent.
7) The pharmaceutical composition of claim 1, wherein the muscle relaxant is selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol [~~(SOMA®)~~], chlorphenesin, chlorphenesin carbamate, chlorzoxazone [~~(PARAFON FORTE®)~~], chlormezanone, cyclobenzaprine [~~(FLEXERIL®)~~], dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone [~~(SKELAXIN®)~~], methocarbamol [~~(ROBAXIN®)~~], metocurine iodide, orphenadrine [~~(NORFLEX®)~~], pancuronium, papaverine, pipecuronium, pridinol [~~(pridinolum)~~], succinylcholine, theophylline,

tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.

8) The pharmaceutical composition of claim 1, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib ~~[(VIOXX™, MK-0966)]~~, celecoxib ~~[(CELEBREX™, SC-58635)]~~, flosulide ~~[(CGP-28238)]~~, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid ~~[(6-MNA)]~~, nabumetone ~~[(prodrug for 6-MNA)]~~, etodolac, nimesulide, SC-5766, SC-58215, T-614, and combinations thereof.

~~[9) A method of treating pain in a mammal comprising the step of administering a pharmaceutical composition according to any one of claims 1-8, wherein the pharmaceutical composition provides therapeutically effective levels of each drug when administered to a mammal.]~~

10) A pharmaceutical dosage form comprising:

a) a therapeutically effective amount of a COX-II inhibitor;

b) a therapeutically effective amount of a muscle relaxant; and

c) at least one pharmaceutical excipient.

11) The pharmaceutical dosage form of claim 10, wherein the dosage form is selected from the group consisting of a gel, cream, ointment, pill, tablet, capsule, liquid, suspension, osmotic device, bead, granule, spheroid, particulate, paste, prill, reconstitutable solid, powder, and injectible liquid.

12) The pharmaceutical dosage form of claim 10, wherein the dosage form independently provides a controlled, delayed, sustained, immediate, timed, slow or rapid release of each of the COX-II inhibitor and the muscle relaxant when exposed to an aqueous environment.

13) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutically effective plasma levels of the COX-II inhibitor for a period up to at least about 12 hours after administration to a subject.

14) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutically effective plasma levels of the muscle relaxant for a period of time after administration to a subject sufficient to enhance the therapeutic benefit provided by the COX-II inhibitor.

15) The pharmaceutical dosage form of claim 10, wherein the pharmaceutical dosage form is adapted for oral, buccal, ocular, otic, gastrointestinal, dermal, rectal, vaginal, cervical, intrauterine, epidermal, transdermal, implant, mucosal, parenteral, sublingual, nasal, or pulmonary delivery.

16) The pharmaceutical dosage form of claim 10, wherein the muscle relaxant is selected from the group consisting of alcuronium, alosetron, aminophylline, baclofen, carisoprodol ~~(SOMA®)~~, chlorphenesin, chlorphenesin carbamate, chlorzoxazone ~~(PARAFON FORTE®)~~, chlormezanone, cyclobenzaprine ~~(FLEXERIL®)~~, dantrolene, decamethonium, diazepam, dyphylline, eperisione, ethaverine, gallamine triethiodide, hexafluorenium, mephenesin, metaxalone ~~(SKELAXIN®)~~, methocarbamol ~~(ROBAXIN®)~~, metocurine iodide, orphenadrine ~~(NORFLEX®)~~, pancuronium, papaverine, pipecuronium, pridinol ~~(pridinolum)~~, succinylcholine, theophylline, tizanidine, tolperisone, tubocurarine, vecuronium, idrocilamide, ligustilide, cnidilide, and senkyunolide.

17) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor is selected from the group consisting of rofecoxib ~~(VIOXX™, MK-0966)~~, celecoxib ~~(CELEBREX™, SC-58635)~~, flosulide ~~(CGP-28238)~~, NS-398, DUP-697, meloxicam, 6-methoxy-2-naphthylacetic acid ~~(6-MNA)~~, nabumetone ~~(prodrug for 6-MNA)~~, etodolac, nimesulide, SC-5766, SC-58215, T-614, and combinations thereof.

18) The pharmaceutical dosage form of claim 10, wherein each drug is released rapidly and the dosage form provides therapeutically effective levels of each drug for a period of at least 12 hours after administration to a subject.

19) The pharmaceutical dosage form of claim 18, wherein the period is about 12 to 60 hours.

20) The pharmaceutical dosage form of claim 19, wherein the period is about 12 to 30 hours.

21) The pharmaceutical dosage form of claim 19, wherein the period is about 18 to 48 hours.

22) The pharmaceutical dosage form of claim 10, wherein the plasma level of ~~one drug~~ the COX-II inhibitor or muscle relaxant is dependent upon the plasma level of the ~~other drug~~ muscle relaxant or COX-II inhibitor, respectively. after administration to a subject

23) The pharmaceutical dosage form of claim 10, wherein the plasma level of [~~one drug~~] is independent of the plasma level of the [~~other drug~~].

24) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutic plasma levels for the muscle relaxant in an amount sufficient to provide a therapeutic benefit to a subject to whom it is administered.

25) The pharmaceutical dosage form of claim 10, wherein the dosage form provides therapeutic plasma levels for the COX-II inhibitor [~~generally~~] in the range of about 90 ng to about 300 ng per ml of plasma.

26) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released sequentially.

27) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released concurrently.

28) The pharmaceutical dosage form of claim 10, wherein the COX-II inhibitor and muscle relaxant are released in spaced apart periods of time.

29) The pharmaceutical dosage form of claim 10, wherein each drug is independently released according to a rapid, immediate, controlled, sustained, slow, timed, targeted, pseudo-first order, first order, pseudo-zero order, zero-order, [~~second-order~~] and/or delayed release profile.

30) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the COX-II inhibitor and a controlled release of the muscle relaxant.

31) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the COX-II inhibitor and a rapid release of the muscle relaxant.

32) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a controlled release of the muscle relaxant and a rapid release of the COX-II inhibitor.

33) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the COX-II inhibitor and of the muscle relaxant.

34) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the muscle relaxant and a delayed but rapid release of the COX-II inhibitor.

muscle relaxant or COX-II inhibitor, respectively

after administration to a subject

the COX-II inhibitor or muscle relaxant

after administration to a subject

in the subject.

after exposure to an aqueous environment

after exposure to an aqueous environment

after exposure to an aqueous environment

after exposure to an aqueous environment.

after exposure to an aqueous environment

after exposure to an aqueous environment

after exposure to an aqueous environment

after exposure to an aqueous environment

after exposure to an aqueous environment

35) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the muscle relaxant and a timed but controlled release of the COX-II inhibitor after exposure to an aqueous environment

36) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the COX-II inhibitor and a delayed but rapid release of the muscle relaxant after exposure to an aqueous environment

37) The pharmaceutical dosage form of claim 10, wherein the dosage form provides a rapid release of the COX-II inhibitor and a timed but controlled release of the muscle relaxant after exposure to an aqueous environment

38) The pharmaceutical dosage form of claim 10, wherein the weight ratio of COX-II inhibitor to muscle relaxant varies from 12.5:2.2 to 50:8.

~~39) A method of treating pain in a mammal comprising the step of administering a dosage form according to any one of claims 10-38, wherein the dosage form provides therapeutically effective levels of each drug when administered to a mammal.~~